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# New and Notable

## Nanoscopic Injury with Macroscopic Consequences: Tau Proteins as Mediators of Diffuse Axonal Injury

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Almost every structure breaks differently when it is pulled faster than a certain threshold, and organs, tissues, and cells are no exception. For delicate, hierarchical structures such as the brain and brain parenchyma, rate-dependent injury mechanisms and criteria have proven difficult to identify with certainty. At the level of the entire head, the most detailed information available comes from tagged magnetic resonance imaging of the brain moving while the head decelerates, but these data are obviously limited to very low physiologic levels of acceleration (1). These data show that, for low-level skull decelerations, strain levels and strain rates in the brain are elevated in regions of stiffer structural attachment between the brain and the skull, largely the same regions where the diffuse axonal injury associated with concussion arises. However, injury mechanisms and thresholds continue to be a source of vigorous debate, as do the types of loading that are most injurious, such as side-to-side shearing versus head-on impact. Macroscopic relationships between likelihood of injury and role of linear versus angular motion of the skull have been assembled painstakingly from indirect data (2), but the biophysical foundation for this at the levels of tissues and cells continues to be a subject of inquiry.

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For many hierarchical tissues, tools for predicting constitutive response are well advanced (e.g., Stylianopoulos et al. (3)), as is the ability to identify and predict the mechanical environment of individual cells within tissues (4,5). The very first tools are now available to predict strength and toughness across hierarchical levels (6). However, in each case, a number of assumptions must be made and the models must be tailored to preserve the salient biophysics as information is transferred from the nanoscale to the macroscale.

At the levels of cells and subcellular proteins, the salient biophysics is often the set of mechanobiological cues delivered to the cytoskeleton. The rate dependence of a number of important and well-known mechanobiological processes involves Deborah numbers that relate the timescales of microscale cytoskeletal responses to timescales of mechanical loading. In endothelial cells, this ratio is central to normal development and remodeling (7). In fibroblast cells, the actin cytoskeleton responds to stretches at different loading rates with a number of reinforcement mechanisms, the majority of which lead to a strengthening of the actin cytoskeleton (8,9). Striated actomyosin fibers are known to react to elastic interactions (10), and the tradeoff among the kinetic, material, and loading time constants determine cytoskeletal responses. These responses are well characterized by both model and experiment, especially for cells loaded on a two-dimensional substratum (7,11,12). From all of this work arise several highly conserved themes including sacrificial structures to insulate the most critical structures from injury across multiple hierarchies and timescales, and adaptive mechanisms to ensure efficient healing and adaptation after excessive loading.

The mechanisms of rate dependence of injury to the axons, however, are elusive. Injury to these axons is believed to be a primary source of the pathology after concussion-level trauma, and is believed to be a major determinant of adverse outcomes after any injury to the brain (13). However, the mechanism by which these injuries occur is a source of debate, and the powerful toolboxes available for hierarchical biophysics have as a consequence not been harnessed to their fullest to develop predictive tools.

New research from Ahmadzadeh et al. (14) suggests that the primary source of injury might be mediated by mechanics at the nanoscale. Their target is the mechanical action of the tau family of proteins that serve to cross-link and hence stabilize the long microtubules found in axons of the central nervous system. The authors combined atomic force microscopy data for a tau protein with models of microtubule arrangement and mechanics, and, with no additional fitting parameters, found a crossover in the primary deformation mechanism at the critical strain rate that laboratory experiments identify as that associated with disruption of axonal microtubules. At slower loading rates, the viscoelasticity of the tau proteins relieves stresses by allowing microtubules to slip relative to one another; at faster loading rates, this viscoelasticity instead transfers mechanical loads in a way that leads microtubules to break and quickly dissociate. These data strongly support a hypothesis that tau proteins are the nanoscale mediator of the critical rate dependence of brain parenchyma.

In hindsight, their target was logical from the clinical and physical perspectives. Clinically, Magnoni et al. (13) have identified that significantly elevated levels of tau proteins in the cerebrospinal fluid that permeates and bathes the brain are predictive of poor outcomes after severe traumatic brain injury. This is fully consistent with the observations of Ahmadzadeh et al. (14), which predict that tau proteins can survive intact after microtubule

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dissociation associated with diffuse axonal injury. Physically, the most successful structured engineering composite materials rely on stochastic fiber failure and tailored fiber interfaces to prevent stress concentrations from developing into dominant cracks (15). Promotion of diffuse injury of axons to prevent cracklike fronts of disruption is sensible in the context of engineered materials. The identification of a family of proteins responsible for mediating rate dependence and injury severity serves as an important cornerstone of future efforts to identify predictive and diagnostic tools for diffuse axonal injury.

The work leaves many questions unanswered, but provides a valuable framework for refinements. The tau family of proteins has many members with different binding, phosphorylation, and kinetic characteristics, all of which will inject some heterogeneity into the injury phase diagram that arises from the initial work of Ahmadzadeh et al. (14). The work also calls for extensions beyond the specific application to axons. Structurally related hierarchical tissue systems exist throughout the body, for example in partially mineralized tissues at tendon-to-bone attachments consisting of collagen cross-linked by stiff mineral particles (16–18). Here, the links between fibers are stiff and the fibers are viscoelastic, but analogous dissipative processes and randomness might be important for optimal toughening (19,20). The unique analytical unique approach taken by Ahmadzadeh et al. (14) provides a powerful platform for exploring these issues, and more broadly is an exciting new approach for translating nanoscale behavior across hierarchies.

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